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"**Diffuse myocardial fibrosis in patient with diabetes mellitus type-II assessed by Cardiac Magnetic Resonance T1 mapping technique**"

DOTTORANDA

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GENERAL CONTENT

DIABETE MELLITUS

1. DEFINITION AND DESCRIPTION OF DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.

Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Diabetic patients have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories:

- In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by

serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers.

- In type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load. The degree of hyperglycemia (if any) may change over time, depending on the extent of the underlying disease process. A disease process may be present but may not have progressed far enough to cause hyperglycemia. The same disease process can cause impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) without fulfilling the criteria for the diagnosis of diabetes. In some individuals with diabetes, adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucoselowering agents. These individuals therefore do not require insulin. Other individuals who have some residual insulin secretion but require exogenous insulin for adequate glycemic control can survive without it. Individuals with extensive β-cells destruction and therefore no residual insulin secretion require insulin for survival. The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its treatment more than the nature of the process itself.

2. *CLASSIFICATION OF DIABETES MELLITUS AND OTHER CATEGORIES OF GLUCOSE REGULATION*

Assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and many diabetic individuals do not easily fit into a single class. For example, a person with gestational diabetes mellitus (GDM) may continue to be hyperglycemic after delivery and may be determined to have, in fact, type 2 diabetes. Alternatively, a person who acquires diabetes because of large doses of exogenous steroids may become normoglycemic once the glucocorticoids are discontinued, but then may develop diabetes many years later after recurrent episodes of pancreatitis. Another example would be a person treated with thiazides who develops diabetes years later. Because thiazides in themselves

seldom cause severe hyperglycemia, such individuals probably have type 2 diabetes that is exacerbated by the drug. Thus, for the clinician and patient, it is less important to label the particular type of diabetes than it is to understand the pathogenesis of the hyperglycemia and to treat it effectively.

Type 1 diabetes (β-cells destruction, usually leading to absolute insulin deficiency) Immune-mediated diabetes.

This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulindependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These HLA-DR/DQ alleles can be either predisposing or protective. In this form of diabetes, the rate of β-cells destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years; such individuals eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide. Immunemediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. Autoimmune destruction of β-cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia. Idiopathic diabetes. Some forms of type 1 diabetes have no known etiologies. Some of these patients have

permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this category, of those who do, most are of African or Asian ancestry. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated. An absolute requirement for insulin replacement therapy in affected patients may come and go.

Type 2 diabetes (ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance).

This form of diabetes, which accounts for 90–95% of those with diabetes, previously referred to as non-insulindependent diabetes, type II diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Ketoacidosis seldom occurs spontaneously in this type of diabetes; when seen, it usually arises in association with the stress of another illness such as infection. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the higher blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their β-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia,

and its frequency varies in different racial/ ethnic subgroups. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 diabetes. However, the genetics of this form of diabetes are complex and not clearly defined.

Other specific types of diabetes.

Genetic defects of the β-cells.

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturityonset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at six genetic loci on different chromosomes have been identified to date. The most common form is associated with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell. Thus, glucokinase serves as the "glucose sensor" for the β-cell. Because of defects in the glucokinase gene, increased plasma levels of glucose are necessary to elicit normal levels of insulin secretion. The less common forms result from mutations in other transcription factors, including HNF-4, HNF-1□, insulin promoter factor (IPF)-1, and NeuroD1. Point mutations in mitochondrial DNA have been found to be associated with diabetes mellitus and deafness. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition. An identical lesion occurs in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome); however, diabetes is not part of this syndrome, suggesting different phenotypic expressions of this genetic lesion. Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism.

Genetic defects in insulin action.

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. Some individuals with these mutations may have acanthosis nigricans. Women may be virilized and have enlarged, cystic ovaries. In the past, this syndrome was termed type A insulin resistance. Leprechaunism and the Rabson-Mendenhall syndrome are two pediatric syndromes that have mutations in the insulin receptor gene with subsequent alterations in insulin receptor function and extreme insulin resistance. The former has characteristic facial features and is usually fatal in infancy, while the latter is associated with abnormalities of teeth and nails and pineal gland hyperplasia. Alterations in the structure and function of the insulin receptor cannot be demonstrated in patients with insulin resistant lipoatrophic diabetes. Therefore, it is assumed that the lesion(s) must reside in the postreceptor signal transduction pathways.

Diseases of the exocrine pancreas.

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. With the exception of that caused by cancer, damage to the pancreas must be extensive for diabetes to occur; adrenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cells mass. If extensive enough, cystic fibrosis and hemochromatosis will also damage β-cells and impair insulin secretion. Fibrocalculous pancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

Endocrinopathies.

Several hormones (e.g., growth hormone, cortisol, glucagon, epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with pre-existing defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved. Somatostatinoma- and aldosteronoma-induced hypokalemia can cause

diabetes, at least in part, by inhibiting insulin secretion. Hyperglycemia generally resolves after successful removal of the tumor.

Drug- or chemical-induced diabetes.

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells. There are also many drugs and hormones that can impair insulin action (i.e. nicotinic acid and glucocorticoids). Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency.

Infections.

Certain viruses have been associated with β-cells destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

Uncommon forms of immune-mediated diabetes.

In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD autoantibodies, and approximately one-third will develop diabetes. Anti–insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues. However, in some cases, these antibodies can act as an insulin agonist after binding to the receptor and can thereby cause hypoglycemia. Anti–insulin receptor antibodies are occasionally found in patients with systemic lupus erythematosus and other autoimmune diseases. As in other states of extreme insulin resistance, patients with anti–insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

Other genetic syndromes sometimes associated with diabetes.

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus.

These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness.

Gestational diabetes mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. GDM complicates 4% of all pregnancies in the U.S., resulting in 135,000 cases annually. The prevalence may range from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes. Deterioration of glucose tolerance occurs normally during pregnancy, particularly in the 3rd trimester.

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)

The Expert Committee (1,2) recognized an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having fasting plasma glucose (FPG) levels ≥100 mg/dl (5.6 mmol/l) but <126 mg/dl (7.0 mmol/l) or 2-h values in the oral glucose tolerance test (OGTT) of ≥140 mg/dl (7.8 mmol/l) but <200 mg/dl (11.1 mmol/l). Thus, the categories of FPG values are as follows:

● FPG <100 mg/dl (5.6 mmol/l) = normal fasting glucose;

● FPG 100–125 mg/dl (5.6–6.9 mmol/ l) = IFG (impaired fasting glucose);

● FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described below).

The corresponding categories when the OGTT is used are the following:

● 2-h postload glucose <140 mg/dl (7.8 mmol/l) = normal glucose tolerance;

● 2-h postload glucose 140–199 mg/dl (7.8–11.1 mmol/l) = IGT (impaired glucose tolerance);

● 2-h postload glucose ≥200 mg/dl (11.1 mmol/l) = provisional diagnosis of diabetes (the diagnosis must be con- firmed, as described below).

Patients with IFG and/or IGT are now referred to as having “pre-diabetes” indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and/or low-HDL type, and hypertension. It is worth mentioning that medical nutrition therapy aimed at producing 5–10% loss of body weight, exercise, and certain pharmacological agents have been variably demonstrated to prevent or delay the development of diabetes in people with IGT; the potential impact of such interventions to reduce cardiovascular risk has not been examined to date. Note that many individuals with IGT are euglycemic in their daily lives. Individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized OGTT.

3. DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

Three ways to diagnose diabetes are possible, and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods given in Table 1. The use of the hemoglobin A1c (A1C) for the diagnosis of diabetes is not recommended at this time. Diagnosis of GDM The criteria for abnormal glucose tolerance in pregnancy are those of Carpenter and Coustan. Recommendations from the American Diabetes Association’s Fourth International WorkshopConference on Gestational Diabetes Mellitus held in March 1997 support the use of the Carpenter/Coustan diagnostic criteria as well as the alternative use of a diagnostic 75-g 2-h OGTT. These criteria are summarized below. Testing for gestational diabetes. Previous recommendations included screening for GDM performed in all pregnancies. However, there are certain factors that place women at lower risk for the development of glucose intolerance during pregnancy, and it is likely not costeffective to screen such patients. Pregnant women who fulfill all of these criteria need not be screened for GDM. This low-risk group comprises women who

- are <25 years of age
- are a normal body weight
- have no family history (i.e., first-degree relative) of diabetes
- have no history of abnormal glucose metabolism

● have no history of poor obstetric outcome

● are not members of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, Pacific Islander).

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk of GDM (marked obesity, personal history of GDM, glycosuria, or a strong family history of diabetes) should undergo glucose testing (see below) as soon as feasible. If they are found not to have GDM at that initial screening, they should be retested between 24 and 28 weeks of gestation. Women of average risk should have testing undertaken at 24 –28 weeks of gestation. A fasting plasma glucose level >126 mg/dl (7.0 mmol/l) or a casual plasma glucose >200 mg/dl (11.1 mmol/l) meets the threshold for the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, the diagnosis must be confirmed on a subsequent day. Confirmation of the diagnosis precludes the need for any glucose challenge. In the absence of this degree of hyperglycemia, evaluation for GDM in women with average or high-risk characteristics should follow one of two approaches.

One-step approach: perform a diagnostic OGTT without prior plasma or serum glucose screening. The one-step approach may be cost-effective in high-risk patients or populations (e.g., some NativeAmerican groups).

Two-step approach: perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test [GCT]) and perform a diagnostic OGTT on that subset of women exceeding the glucose threshold value on the GCT. When the two-step approach is used, a glucose threshold value >140 mg/dl (7.8 mmol/l) identifies 80% of women with GDM, and the yield is further increased to 90% by using a cutoff of >130 mg/dl (7.2 mmol/l). With either approach, the diagnosis of GDM is based on an OGTT. Diagnostic criteria for the 100-g OGTT are derived from the original work of O'Sullivan and Mahan (4) modified by Carpenter and Coustan (3) and are shown in the top of Table 3. Alternatively, the diagnosis can be made using a 75-g glucose load and the glucose threshold values listed for fasting, 1 h, and 2 h (Table 2, bottom); however, this test is not as well validated as the 100-g OGTT.

Table 1. Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration >200 mg/dl (11.1 mmol/ l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. or 2. FPG <126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.
3. or 3. 2-h postload glucose >200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.
Diagnosis and Classification DIABETES CARE, VOLUME 27, SUPPLEMENT 1, JANUARY 2004

THE IMPACT OF DM ON THE HEART: DIABETIC CARDIOMYOPATHY

It has been well established the association of diabetes with hypertension, obesity and coronary heart disease and predisposes diabetic subjects to heart failure (HF). This has been linked to duration of diabetes and the extent of glycemic control. Cardiovascular morbidity and mortality in diabetes are strikingly high with a reduction in life expectancy.

It has been recently shown that individuals in their sixties who have a combination of diabetes and heart disease have an average reduction in life expectancy of about 15 years. Four decades ago the Framingham study firmly established the epidemiologic link between diabetes and HF, showing that diabetes predicted heart failure independent of hypertension, age, obesity, dyslipidemia and coronary disease.

It is now recognized that in addition to accelerating and worsening the consequences of coronary artery disease and hypertension, diabetes also has a direct effect on the myocardium, placing the diabetic subject at an increased risk of developing heart failure.

Diabetes increases the odds of a non-ischemic dilated cardiomyopathy (odds ratio: 1.75; 95% CI: 1.71-1.79), which has been associated with increased myocardial stiffness. This entity of a unique diabetic cardiomyopathy (DMCMO) was originally proposed by Lundbeek and subsequently confirmed at autopsy by Rubler et al in 1972 in four diabetic patients who presented with heart failure (HF) and showed no evidence of hypertension (HT), CAD, or valvular disease. Rubler found evidence of myocardial hypertrophy, fibrosis, and microvascular changes in keeping with dilated cardiomyopathy. The development of myocardial dysfunction in diabetes has been attributed to

the effects of lipotoxicity, microvascular AGEs deposition, microvascular rarefaction, and autoimmunity, all of which contribute to produce myocardial fibrosis and/or myocardial hypertrophy, the hallmarks of DMCMO that are described below (Table 2).

Table 2. Contribution of pathophysiological mechanisms to the phenotypes of diabetic cardiomyopathy

Metabolic overload effects	HFPEF	HFREF
Insulin resistance/hyperinsulinemia	+++	+
Hyperglycemia	+++	+
Lipotoxicity & oxidative stress	+++	+
AGEs deposition	+++	+++
Microvascular rarefaction	+++	+++
Autoimmunity	-	+++
Structural changes	Functional effects	
Stimulus to ventricular remodeling	Endothelial dysfunction	Autoimmune cell de
Effects of microvascular dysfunction	Low NO availability	Hypoxic damage
Cardiomyocyte changes	Hypertrophy & stiffening	Stiffening & apoptos
Myocardial matrix changes	AGEs +reactive fibrosis	AGEs + replacement
	Diastolic dysfunction	Systolic dysfunction

Diabetic cardiomyopathy has been previously differentiated into two phenotypes:

- restrictive or heart failure with preserved left ventricular ejection fraction (HFPEF)
- dilated or heart failure with impaired or reduced left ventricular ejection fraction (HFREF).

The phenotype-specific pathophysiological mechanisms for the DCM phenotypes proposed for left ventricular (LV) remodeling and dysfunction consist of coronary microvascular endothelial dysfunction and cardiomyocyte cell death for HFPEF and HFREF, respectively. Similarly, the preference of endothelial or cardiomyocyte cell compartments in DM patients could explain the development of DCM into two subtypes, restrictive/HFPEF or dilated/HFREF phenotypes. Diabetes mellitus-induced metabolic derangements such as hyperglycemia, lipotoxicity, and hyperinsulinemia favor development of DCM with the restrictive/HFPEF type, which is more prevalent in obesity. In contrast, autoimmunity predisposes to the dilated/HFREF phenotype, which manifests itself more in type 1 DM. Finally, coronary microvascular rarefaction and advanced glycation end products (AGEs) deposition are relevant pathognomic abnormalities in both phenotypes.

1. Pathogenetic mechanisms of myocardial dysfunction in diabetes

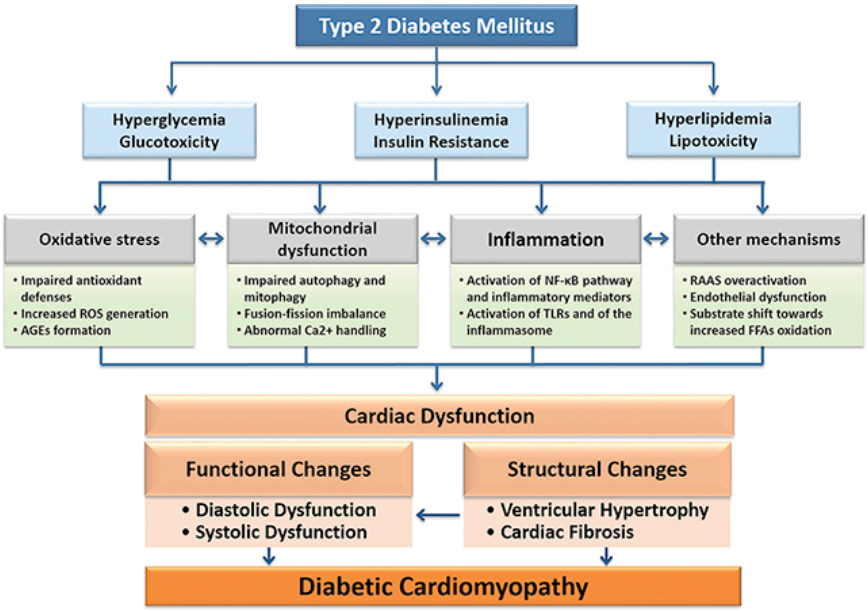
Role of hyperglycemia

Hyperglycemia (Figure 1) increases the level of free fatty acids and growth factors in the myocardium, and causes abnormalities in substrate supply and utilization. Furthermore, it is toxic to the endothelial cell, causes mitochondrial damage and induces oxidative stress and the release of superoxides, leading to abnormal gene expression, impaired production of nitric oxide (NO) and reduced distensibility of cardiomyocytes.

Hyperglycemia activates the renin-angiotensin system in myocardial cells (Figure 1) leading to cell growth and cardiac hypertrophy and these damaging effects can be further aggravated by oxidative stress. In addition, it stimulates collagen production and crosslinking as well as the production and deposition of non-enzymatic formation of advanced glycation end-products (AGEs) in the coronary microvasculature and the myocardial interstitium. AGEs trigger vascular inflammation, lower myocardial NO bioavailability and contribute to concentric LV remodeling. AGEs-induced crosslinking in collagen and elastin and result in increased myocardial stiffness and

impaired cardiac relaxation in the diabetic heart that has been correlated with tissue Doppler indices of diastolic dysfunction.

Figure 1. Cardiometabolic mechanisms in myocyte injury.



Insulin resistance/hyperinsulinemia

Insulin resistance (IR) affects a number of signaling pathways, causing cardiomyocyte hypertrophy, reactive interstitial fibrosis and expression of myocardial titin, all of which contribute to the reduction in cardiomyocyte distensibility. Central obesity (associated with IR) and microvascular rarefaction cause the release of proinflammatory cytokines and the generation of reactive oxygen species (ROS), leading to an inflammatory state in the coronary microvasculature with a reduction in nitric oxide (NO) bioavailability, increased vessel permeability and programmed cell death (apoptosis). This coronary microvascular endothelial dysfunction is thought to drive the development of myocyte hypertrophy with concentric remodeling and myocardial stiffening resulting in LV diastolic dysfunction.

Lipotoxicity and mitochondrial dysfunction

Insulin resistance results in a reduction of myocardial energy supply due to changes in substrate utilization from glucose to free fatty acids. It impairs myocardial glucose utilization and leads to excess fatty acid uptake into cardiomyocytes and eventually induces mitochondrial dysfunction, reduction in ATP availability and eventual cell death (lipotoxicity). The defect in myocardial energy

production impairs myocyte contractile function, manifesting initially as diastolic function. Excess myocardial triglyceride content (myocardial steatosis) is demonstrable on proton-MR spectroscopy and has been correlated with echocardiographic left ventricular diastolic dysfunction as well as with longitudinal strain measurements.

Impaired coronary flow reserve in diabetes

Several factors: reduced NO production, AGEs- mediated stiffening of coronary media, and perivascular fibrosis, contribute to a reduction in coronary flow reserve. In addition, cardiomyocyte hypertrophy is associated with a reduction in capillary density (microvascular rarefaction) that leads to impaired myocardial perfusion, lowers NO bioavailability and contributes to myocardial stiffness that is typical of diastolic dysfunction. Tissue hypoxia results in the further release of ROS leading to myocyte cell death (apoptosis) and a decline in systolic function accompanied by remodeling with ventricular dilatation.

Microvascular disease and ischemia

Microangiopathy, characterized by thickening of the capillary basement membrane and the media of the arteriole, and associated with perivascular fibrosis, has been observed in autopsy samples of diabetic patients. Microaneurysms and spiral deformation of microvessels in the myocardium of type 2 DM, similar to retinal vascular changes of diabetes, have also been described. It has been shown that expression of vascular endothelial cell growth factor (VEGF) in the heart is downregulated in diabetes and that this downregulation is closely associated with the reduction in capillary density, apoptosis of endothelial cells and interstitial fibrosis.

The microangiopathy in diabetes explains why microalbuminuria/proteinuria is not only associated with nephropathy, but with widespread microvascular disease, including the heart. In the heart, diabetic autonomic neuropathy contributes to impaired autoregulation and lack of flow reserve, a factor that may account for increased rates of sudden cardiac death as well as a higher overall cardiovascular mortality rate in diabetic patients.

Autoimmunity

In type 1 DM subjects, cardiac myosin autoantibody and troponin T release are thought to trigger an immune response leading to myocyte cell death and replacement fibrosis. It has been proposed that this immune response, combined with the effects of worsening tissue hypoxia described above, probably provide the stimulus to the development of eccentric ventricular remodeling,

resulting in ventricular dilatation and systolic dysfunction leading to the picture of dilated cardiomyopathy that has been described in type 1DM.

2. Development of myocardial dysfunction

As explained above, excess chronic oxidative stress produced by the release of ROS from the mitochondria and from proinflammatory cytokines and leucocytes, cause direct damage to plasma membrane cell organelles leading to myocardial damage. This may account for the increased oxidative injury resulting in the excessive morbidity and mortality after myocardial infarction in patients with diabetes when compared to patients without diabetes. Oxidative stress is the unifying factor in the development of diabetes-related cardiac complications, including atherosclerosis (Figure 1).

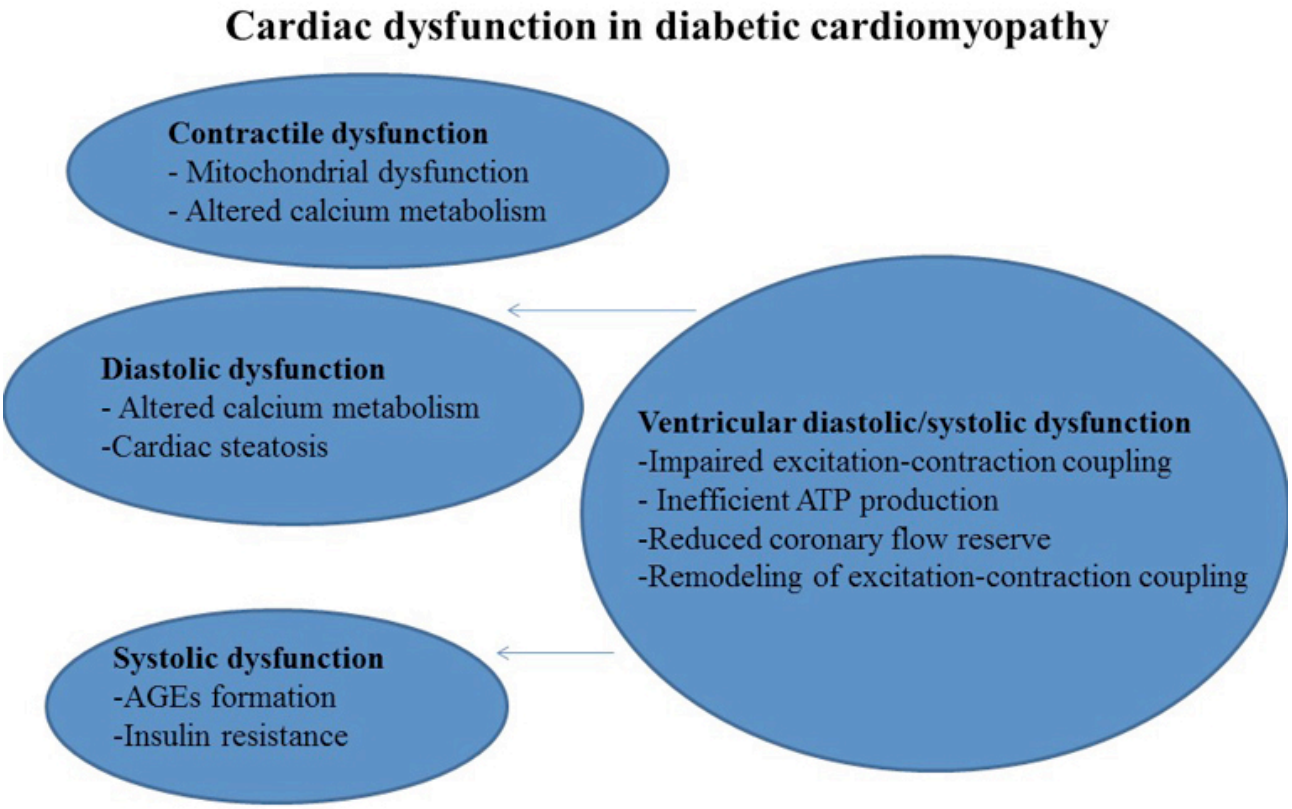
Myocardial damage in the absence of epicardial coronary disease (macrovascular) is most likely related to microvascular dysfunction, leading to diabetic cardiomyopathy (DMCMO).

Recent evidence has shown that insulin resistance-induced arterial stiffness in normotensive subjects contributes to diastolic dysfunction independent of age, blood pressure and body mass index. Together with activation of the sympathetic nervous system, the increase in afterload and impaired ventricular-vascular coupling as a result of arterial stiffness increase likelihood of heart failure development in these subjects.

Based on the fact that subjects with diastolic dysfunction have more LV hypertrophy and stiffness (attributed to AGEs deposition and stiff cardiomyocytes), while subjects with systolic dysfunction have a dilated left ventricle (following cardiomyocyte cell death and replacement fibrosis), a new model of diabetic cardiomyopathy has been proposed. In a recent review Seferovic and Paulus proposed that the deposition of AGEs in the myocardium and coronary microvascular rarefaction contribute to both diastolic and systolic dysfunction. Hyperglycemia, lipotoxicity, and hyperinsulinemia lead to myocyte hypertrophy, increased diastolic stiffness and the development of the restrictive/HFPEF phenotype, typical in obese type 2 DM patients (Figure 1). Autoimmunity with myocyte cell death leads to the dilated/HFREF phenotype that is more prevalent in type 1 DM patients. In this model, more selective involvement of endothelial cells in the coronary microvasculature drives the progression to diastolic dysfunction, while cardiomyocyte damage and ensuing myocyte loss trigger eccentric remodeling and decline in systolic function.

Changes in biventricular cardiac function in diabetic cardiomyopathy are summarized in Figure 2.

Figure 2. Cardiac Dysfunction in diabetic cardiomyopathy



3. Epidemiology

Because of the structural and functional changes that occur in DMCMO, subjects develop functional changes early in the course of their disease. Diastolic dysfunction is the most frequent echocardiographic finding in both type 1 DM and type 2 DM patients and precedes the development of symptoms. The prevalence of asymptomatic diastolic abnormalities detected on TDI in a population-based study is high (23%) with over a third developing heart failure at 5 years. In the early stages of type 1 DM, subclinical myocardial dysfunction is frequent, but clinical signs of heart failure are infrequent and developed in 3.7% of subjects over a 12-year follow-up period in one study. Subjects who developed heart failure were older and had a longer duration of diabetes (35±9 years); they had higher blood pressure and a higher prevalence of albuminuria and

retinopathy than those without heart failure. Diabetic patients with microvascular complications showed the strongest association with cardiomyopathy and this relationship paralleled the duration and severity of hyperglycemia. These findings have been confirmed in a recent large case-controlled study from the Swedish national registry that showed a fourfold increase in the risk of heart failure in type 1 DM, especially in subjects with poor glycemic control and impaired renal function.

4. Clinical markers and implications for treatment

Asymptomatic diastolic dysfunction offers an opportunity for the primary prevention of heart failure in at-risk diabetic subjects if changes can be detected early and appropriate therapy instituted. Since there is little evidence to support the use of biomarkers in detecting the early stages of DMCMO, a strategy of screening asymptomatic diabetic subjects for impaired LV function with natriuretic peptides is not recommended. It is suggested that diabetic subjects at risk of developing DMCMO (such as those with atrial fibrillation, microalbuminuria/proteinuria, autonomic neuropathy, retinopathy, metabolic syndrome) should undergo non-invasive imaging using tissue Doppler imaging and strain rate imaging as well as magnetic resonance spectroscopy, to enable early detection of DMCMO.

Subclinical changes of diastolic dysfunction has been demonstrated across the spectrum of IR and may present before the onset of diabetes, presenting an even larger disease burden for primary prevention of heart failure in diabetes. There is evidence that glycemic control and lifestyle measures started earlier in the course of the IR spectrum (early diabetes, prediabetes and metabolic syndrome) could address the metabolic milieu before they have become established and may be beneficial. In this respect the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study has shown that intensive treatment of hyperglycemia, targeting glycated hemoglobin levels below 7%, when initiated early in patients with short duration of diabetes and low cardiovascular risk, results in a significant 42% reduction of cardiovascular events in the long term.

The diagnosis of diabetic cardiomyopathy may be suspected when myocardial disease in patients with diabetes cannot be attributed to any other known cardiovascular disease. Metabolic and microvascular mechanisms contribute to the pathogenesis. At a subcellular level in the mitochondrion, oxidative stress, coupled with loss of normal microvessels and remodeling of the

extracellular matrix, lead to an inflammatory state with decline in cardiomyocyte contractile function. The disease course consists of a hidden subclinical period, during which endothelial dysfunction drives the cellular and matrix changes that result in diastolic stiffness, while autoimmune responses result in myocyte loss and decline in systolic function.

Subjects at risk of DMCMO are those with a long duration of poorly controlled diabetes, evidence of microvascular disease elsewhere, atrial fibrillation and those with markers of insulin resistance such as central obesity and metabolic syndrome.

5. Diagnostic approach

Diagnosis of DCM requires impairment of the glucose metabolism and a thorough approach to exclude other causes of ventricular dysfunction such as coronary, valvular, hypertensive, or congenital heart disease and infections such as viral myocarditis or toxins-induced, familial or infiltrative cardiomyopathies. Although the chief cause of DCM is diabetes, the following risk factors which might exacerbate DCM need special attention: obesity, chronic high blood glucose, high blood pressure, dyslipidemia, smoking and alcohol consumption.

A relevant diagnostic approach should be employed to diagnose DCM, which should include a thorough history and a proper physical examination: relevant investigative approach including urine analysis to test for the presence of proteinuria, stress test, chest X-ray, electrocardiography and echocardiography (Table 3). Invasive measures should also be considered in some situations including myocardial biopsy, cardiac catheterization to evaluate cardiac chamber blood flow, pressures and coronary blood flow.

Table 3. Diagnostic approaches employed in the diagnosis of DCM.

Diagnostic tool	Parameters and implications
Clinical	• History of DM, DCM and family history of diabetes. • Physical examination, evaluation of symptoms and complications
Biochemistry	• Urine, for proteinuria • Serum aminoterminal propeptide of type I and type III collagens, and carboxyterminal telopeptide of type I collagen • B-natriuretic peptide (BNP), for increased ventricular pressure or heart failure
Transthoracic echocardiography	• Transmitral Doppler analysis, for left ventricular mass and diameter • Pulmonary venous blood flow, for diastolic dysfunction • Color M-mode, for diastolic dysfunction • TDI, decreased tissue velocities for both diastolic and systolic dysfunction • TDI, strain and strain rate, for systolic and diastolic dysfunction
Magnetic resonance imaging	• MRI, for left ventricular mass and diameter • Late gadolinium enhancement MRI, for diastolic and systolic dysfunction • Magnetic resonance spectroscopy, for myocardial fibrosis, triglyceride content and myocardial phosphocreatine to ATP ratio
SPECT	• Flow limitation and sarcolemmal membrane integrity • G-SPECT, differentiate ischemic from non-ischemic cardiomyopathy, assess both myocardial perfusion and ventricular function • Quantitative myocardial perfusion SPECT, myocardial and coronary artery disease
PET	Radiotracer kinetics, quantitative assessment of myocardial blood flow

5.1 **Echocardiography**

Although 2D-TTE is cheap and easily accessible, it is hampered by the inability to detect the subtle features of myocardial dysfunction in DM. Newer technologies, such as TDI, look promising as they apply a high-velocity low-amplitude filter to the myocardium, enabling an assessment of myocardial tissue velocities with relative ease. The advantage of TDI over standard Doppler

echocardiographic indices is that the results are independent of changes in ventricular pre-load. However, TDI is unable to differentiate between active contraction and passive movement of a myocardial segment.

Speckle tracking echocardiography (STE)

Strain and strain rate echocardiography is a unique technique for assessing myocardial systolic and diastolic function. STE has improved the quantitative assessment of regional or segmental wall motion and also the accuracy and reproducibility of test readings. STE is a new advanced imaging tool which is highly sensitive and reproducible to evaluate subtle features of ventricular myocardial dysfunction. Changes in ventricular systolic strain and strain rate have the potential ability to discriminate between different myocardial viability states. Measurement of the diastolic rate of deformation can differentiate physiological from pathological hypertrophy and restrictive from constrictive cardiomyopathy.

Contrast echocardiography

Contrast echocardiography is useful in current clinical practice as proper delineation of the endocardial border observed after contrast administration increases the clarity of the images and improves the results provided by the algorithms orientated to the assessment of ventricular motion. Moreover, direct assessment of myocardial blood flow and flow reserve is possible with contrast echocardiography, as microbubble contrast agents remain entirely within the intravascular space. In any myocardial segment, contrast echocardiography denotes the status of microvascular perfusion within that region, which is important in patients with long-standing diabetes. Contrast LV opacification allows more accurate measurements of LV size and mass, and myocardial contrast echocardiography could provide an alternative non-invasive imaging method to evaluate the coronary anatomy to exclude CAD.

Three-dimensional echocardiography

Real-time three-dimensional echocardiography is used in conjunction with strain rates for further evaluation of regional LV systolic and diastolic function. A similar approach could be used to evaluate LV and RV function in patients with long-standing DM or DCM.

5.2 **Computed tomography**

Similarly, coronary artery calcification (CAC) can increase significantly in asymptomatic patients with long-standing type 2 DM compared with non-diabetic subjects. The CAC score, derived originally from electron-beam computed tomography (CT) and more recently from multislice CT, correlates strongly with the presence and severity of histological and angiographic evidence of coronary atherosclerosis and conventional coronary heart disease risk factors, in particular C-reactive protein, reflecting stable and unstable plaques.

5.3 **Magnetic resonance**

Cardiac MRI has recently emerged as a useful imaging tool for structural and functional myocardium disorders. It is also an important non-invasive modality to detect diastolic dysfunction and myocardial steatosis in DM and other pathological myocardial disease.

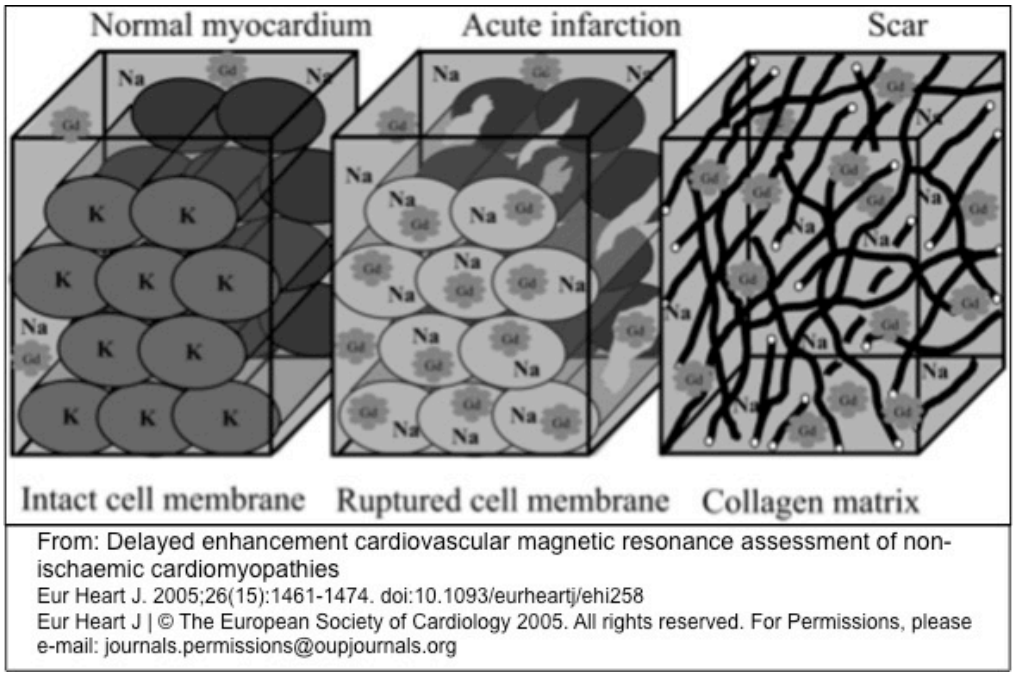
In particular cardiac MR enable to assess the presence of myocardial fibrosis using direct and indirect technique:

1) Direct: LGE and T1 mapping
2) Indirect: Tagging and Feature tracking

Late-Gadolinium Enhancement (LGE)

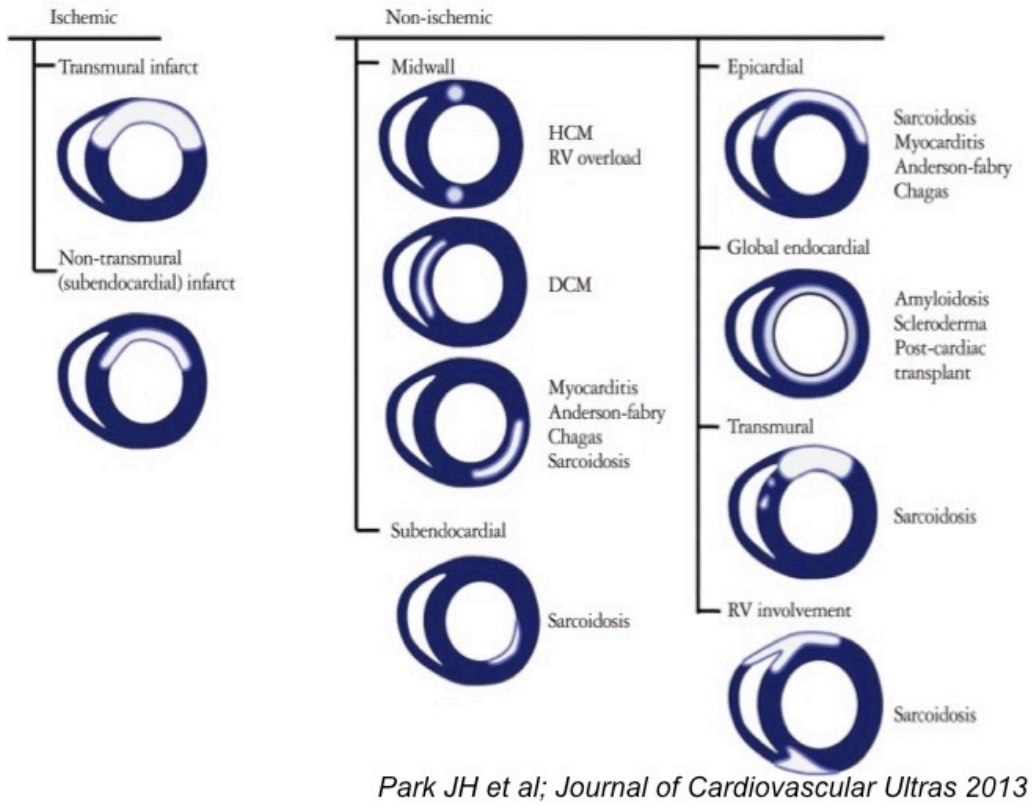
Fibrotic areas within myocardium are identified on CMR by a semiquantitative analysis of the myocardial signal intensity (SI) 10-15 minutes after injection of Gd on Inversion Recovery Gradient Echo T1-weighted images). After nulling the signal of healthy myocardium by an inversion pulse, the fibrosis appears on the LGE images as hyperintense myocardial regions distinguishable by non-injured, healthy, remote myocardium (Figure 3).

Figure 3. Gadolinium in healthy and pathological myocardium



This technique is very effective in the localization and definition of focal fibrosis and it enables to discriminate ischemic from non-ischemic disease (Figure 4).

Figure 4. LGE in ischemic and non-ischemic disease



This technique it does not work equally in the detection of diffuse fibrosis is burden by the operator dependence.

T1 mapping

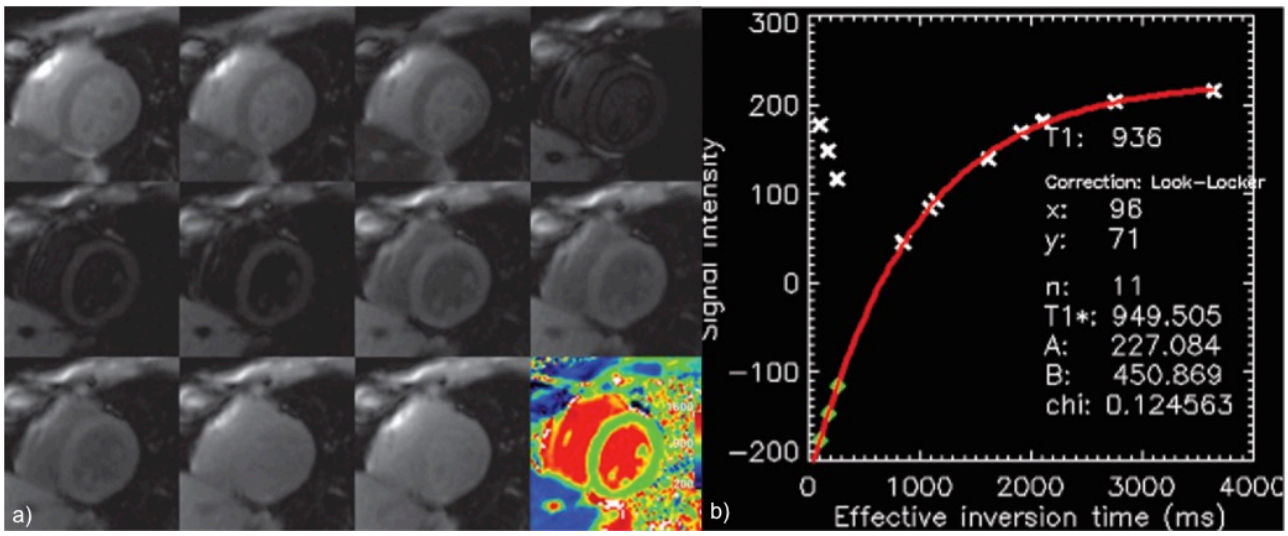
This technique allow signal quantification by the use of standardized reproducible T1 and T2 values (expressed in milliseconds), which appears to be more robust than qualitative assessment of signal intensity.

Nonenhanced T1 Mapping

All tissues have inherent T1 relaxation times that are based on a composite of their cellular and interstitial components (water, protein, fat, and iron content). At a fixed magnetic field strength and in the absence of exogenous contrast agent (i.e. gadolinium chelate), the native T1 value of normal tissue falls within a predictable range (at 1.5 T, normal myocardium has a T1 relaxation time of 940–1000 msec). Whereas qualitative sequences rely on the use of arbitrary signal intensity scales for T1 and T2 values that have inter-patient and inter-image variability, myocardial mapping offers the potential to produce images that have standardized, reproducible scales similar to the attenuation values used at computed tomography.

Mapping sequences employ different techniques (MOLLI, ShMOLLI, SASHA, SAPHIRE sequences) to acquire a series of images at various inversion times, from which a T1 recovery curve is derived. The result is a T1 map, a parametric image that displays the T1 relaxation values pixel by pixel (Figure 5).

Figure 5. Native T1 mapping: a) same plane acquired with different T1 and native T1 map; b) Graph of a curve-fitting analysis for a single pixel. (Courtesy of Hamlin S et al; Radiographics 2014)



These maps are commonly displayed using color to aid in visual interpretation. Regions of interest can be drawn to assess a larger area of the myocardium.

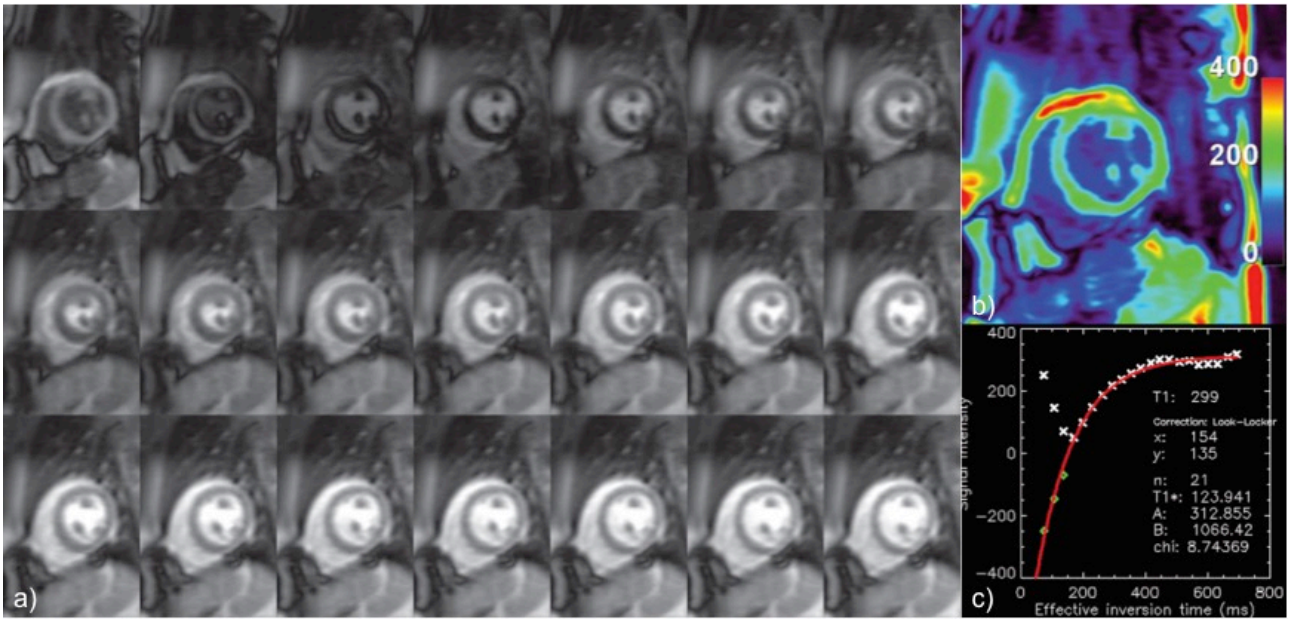
Native myocardial T1 relaxation times vary by magnetic field strength (3-T magnets result in longer native T1 times), equipment manufacturer, and the type of mapping sequence used. Several recent publications have reported “normal” T1 ranges for healthy subjects; these ranges are discussed later in the article. By providing a reproducible standard of T1 and T2 values, myocardial mapping may reduce interpretation variability and error related to subjective analysis and image artifact. Quantitative tissue characterization with mapping may also be better suited for longitudinal assessment of patients with cardiac disease than the arbitrary scale used at traditional cardiac MR imaging.

Myocardial disease affects the cellular and extracellular composition of myocardial tissue, thereby altering the native T1 and T2 signals. In general, a prolonged native myocardial T1 signal is encountered in various disease states that result in edema or fibrosis, and in amyloid deposition. Shortening of the native T1 relaxation time can be seen with siderosis, Anderson-Fabry disease, and fat deposition, although these diseases are less commonly encountered in routine practice.

Contrast-enhanced T1 Mapping

The use of gadolinium-based contrast agents shortens the native T1 relaxation time of myocardium by several hundred milliseconds. Areas with a disproportionate accumulation of contrast material (fibrosis) will therefore exhibit shorter T1 relaxation times than normal myocardium when using contrast-enhanced T1 mapping sequences (Figure 6). Whereas nonenhanced T1 map values are a native property of the myocardium, contrast-enhanced T1 map values are variable and highly dependent on *(a)* variable weight-based contrast agent dosing, *(b)* the exact time elapsed after contrast agent administration before images are acquired, *(c)* renal clearance of the contrast agent, and *(d)* displacement of contrast material by the hematocrit. Thus, nonenhanced T1 mapping is less variable (within the same patient and across patients) than contrast-enhanced T1 mapping because of the variability in the exact time of image acquisition with contrast-enhanced mapping.

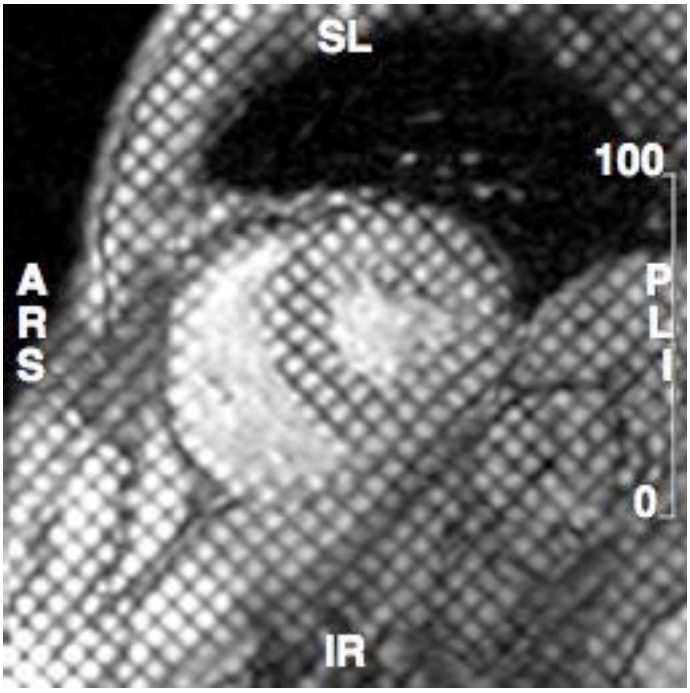
Figure 6. Contrast-enhanced T1 mapping: a) same plane acquired with different T1; b) T1 map; c) Graph of a curve-fitting analysis for a single pixel (Courtesy of Hamlin S et al; Radiographics 2014)



Tagging

In 1988 it was introduced a new CMR technique to magnetically label or tag different regions within the heart wall. The basic idea was to create noninvasive markers within the heart wall by applying saturation planes perpendicular to the imaging plane at the electrocardiographic trigger signal before image acquisition. During the subsequent image acquisition, reduced signal is obtained from the saturated tissue. Therefore, the cut line of the image plane and the saturated plane appears as a hypointense or black line on the images (Figure 7).

Figure 7. Tagging image.



A fast way to generate a tagging pattern was introduced by Axel and Dougherty in 1989. This method is known as spatial modulation of magnetization (SPAMM); it is fast and it can be applied twice, in 2 orthogonal directions, yielding a grid pattern. With SPAMM either sharper stripes or a sinusoidal intensity variation can be obtained.

Because the magnetization is a property of the tissue, the tag lines move along with the tissue in which they are created. When created at end diastole, the lines will deform with the myocardium during contraction, and become undeformed again during subsequent relaxation. From this it can be recognized that the deformed tag pattern reflects the underlying motion of the heart wall. By tracking the motion of the tag lines throughout the cardiac cycle, the intramural myocardial deformation can be quantified. The tags gradually will fade during the cardiac cycle because of tissue T1 relaxation and the imaging radiofrequency pulses. This fading may hamper assessment of regional myocardial function, especially the analysis of the relaxation of the heart during diastole.

Tagged image analysis

The analysis method used to extract information on myocardial function from the tagged images depends on the clinical purpose for which it is applied.

1) Visual assessment requires tags that can be easily followed by eye, and therefore the tag lines should be as sharp as possible. For this purpose image quality is essential, whereas temporal resolution and the applicability of semiautomatic postprocessing become less important. This means for the image acquisition that a rectangular intensity profile of the tag lines is preferred, and that grid-tagged images are presented to the observer.

2) Quantitative assessment of myocardial deformation with (semi)automated analysis methods, however, other types of tagging images may be more suitable.

Basically, 3 types of analysis methods can be discerned:

- The first type of method aims at the detection and tracking of the tag lines in the images (Software programs such as Findtags and SPAMMVU).
- The second type is based on optical flow, a method originating from machine vision applications, which determines the motion of the object in the image by assessing temporal and spatial changes in image intensity.
- The third type is the harmonic phase (HARP) analysis. The HARP method calculates for each pixel the spatial phase in the periodic tagging pattern. This phase can be used to track the points through the cardiac cycle, or to calculate the deformation directly, by calculating the regional spatial frequency of the tagging pattern and comparing it with the undeformed frequency. Because of its almost fully automated nature, HARP is currently the most widely used analysis method.

Strain analysis

Strain analysis describes the change of shape of material (i.e., myocardium) resulting from deformation. Strain is independent of rigid body motion (translation and/or rotation) and does not necessarily need an external reference system.

For interpretation of normal strains, a coordinate system is required. Two different coordinate systems, the radial/fiber/cross fiber system and the radial/circumferential/ longitudinal system, are used for this purpose. Using this coordinate system, myocardial deformation can be described in a more intuitive way:

1) Radial strain, representing deformation of the heart in the radial direction (i.e., toward the

center of the ventricle). Positive radial strain during systole reflects the local contribution of the myocardium to wall thickening, andnegative radial strain during systole implies local wall thinning (dyskinesia);

2) Circumferential strain, reflecting intramural circumferential shortening. A negative value is related to myocyte contraction, and a positive value indicates systolic bulging;

3) Longitudinal strain, reflecting the regional amount of myocardial shortening from base to apex (negative value).

The strain rate can be derived from the different strain measures by dividing strain by the time information (T) from each time frame:

$$\text{Strain rate} = \text{Strain}(t2) - \text{Strain}(t1)/(t2 - t1)$$

Time derivative of strain is the strain rate (1/s) and is of importance in assessing the relaxation of the ventricle. Quantification of the strain rate allows detailed evaluation of left ventricular (LV) diastolic function.

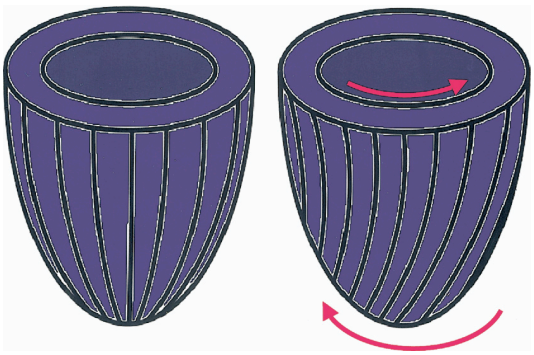
In addition to the normal strains, 3 shear angles can be calculated:

- the radial-circumferential shear angle,
- the radial-longitudinal shear angle,
- the circumferential-longitudinal shear angle.

The circumferential-longitudinal shear angle describes the twisting motion of the heart and is closely related to torsion of the LV.

Cardiovascular magnetic resonance tissue tagging also offers the opportunity to quantify myocardial torsion (Figure 8). Torsion is defined as the circumferential-longitudinal shear on the epicardial surface between 2 short-axis slices. In the LV, torsion and untwisting is the result of contraction and relaxation of the spiraling myofibers.

Figure 8. Ventricular torsion and untwisting. Torsion and untwisting are the result of contraction and relaxation of the spiraling subepicardial and subendocardial myofibers. The net ventricular torsion is the result of the subepicardial contraction and subendocardial counterbalancing contraction.

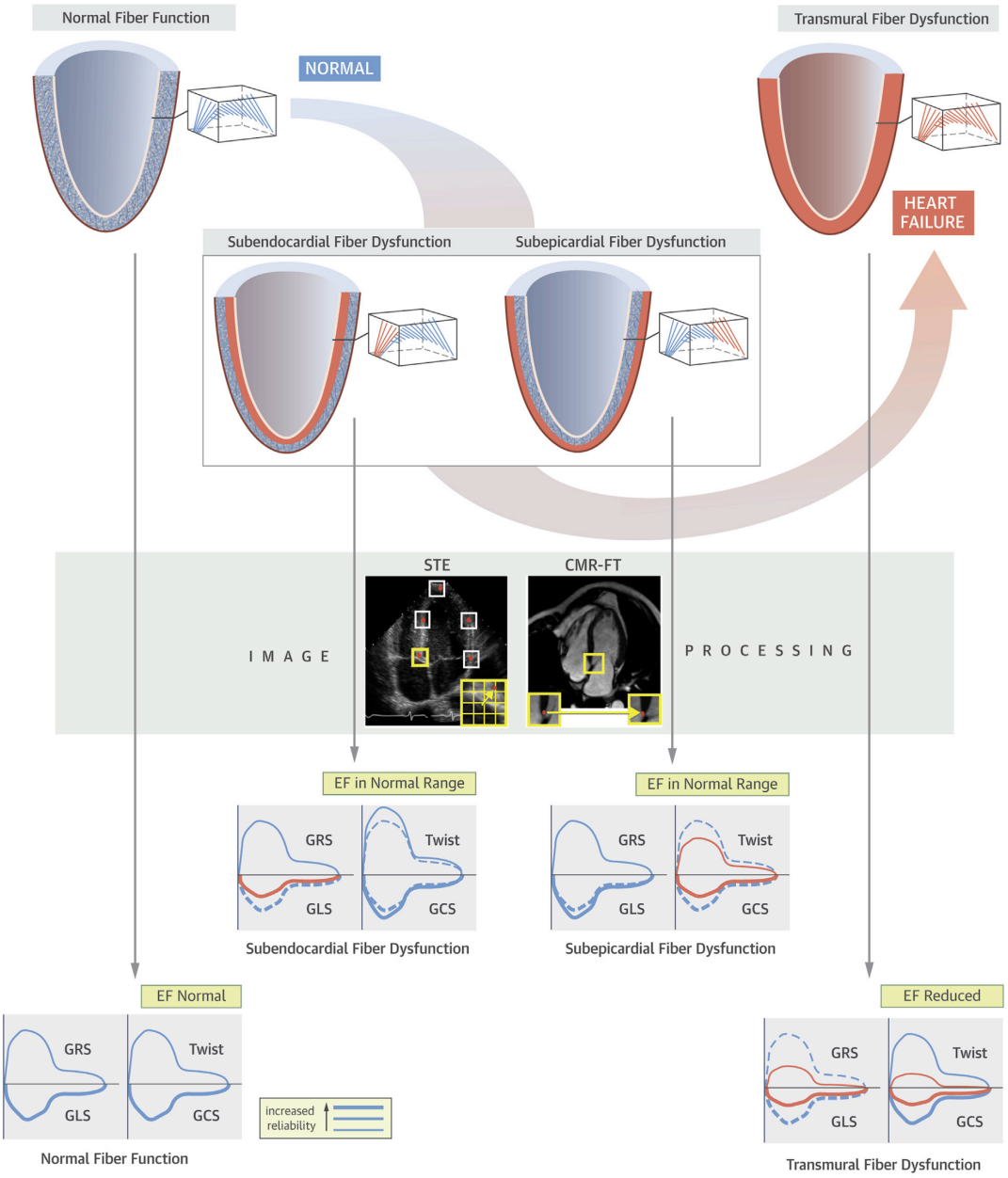


Feature Tracking

FT-CMR has been explored on stacks of 2D cine images, with a typical slice distance of 6 to 8 mm and strong contrast between blood pool and myocardium, but with a lower in-plane spatial (1 to 2 mm) and temporal resolution (commonly 30 phases per heart cycle) than with 2D-STE.

FT-CMR on 2D stacks suffers also from through-plane motion effects. Temporal averaging may result in lower strain values for FTCMR in comparison to STE. Due to the lack of intramyocardial features, FT-CMR algorithms focus on the endocardial and epicardial borders with a stronger weighing of endocardial deformation explaining some of the differences in results found in direct comparisons of FT-CMR and STE (Figure 9).

Figure 9. Tissue Tracking



Claus, P. et al. J Am Coll Cardiol Img. 2015; 8(12):1444–60.

From the displacement estimations provided by these tracking methodologies a series of deformation parameters relevant to assess the mechanics of the myocardium (Table 4).

Table 4. Deformations parameters

	Definition	Parameters
Displacement, cm	Distance between instantaneous and initial (often end-diastolic) position of a myocardial segment	Longitudinal displacement Radial displacement Circumferential displacement
Velocity, cm/s	Velocity of displacement (displacement/time) accuracy is highly frame-rate dependent	Longitudinal velocity Radial velocity Circumferential velocity
Strain, %	Change in length of an object within a certain direction relative to its initial (often end-diastolic) length	Global/segmental longitudinal strain (GLS/LS) Global/segmental radial strain (GRS/RS) Global/segmental circumferential strain (GCS/CS)
Strain rate, 1/s	The speed of deformation accuracy is highly frame-rate dependent	Peak systolic global longitudinal strain rate (GLSR-S) Early diastolic global longitudinal strain rate (GLSR-E) Late diastolic global longitudinal strain rate (GLSR-A) Peak systolic global radial strain rate (GRSR-S) Early diastolic global radial strain rate (GRSR-E) Late diastolic global radial strain rate (GRSR-A) Peak systolic global circumferential strain rate (GCSR-S) Early diastolic global circumferential strain rate (GCSR-E) Late diastolic global circumferential strain rate (GCSR-A)
Rotation	Results from shortening and lengthening of helically oriented myocardial fibers causing counterclockwise rotation of the apex and clockwise rotation of the base as viewed from the apex	Peak systolic apical rotation (apical-R) Peak systolic basal rotation (basal-R) LV twist (LVT) LV torsion (LV-tor) Percentage of LV untwist at mitral valve opening (%LV-UT-MVO) LV untwist rate (LV-UTR) Time to peak untwist (TTP-UT)

LV = left ventricular.

Stress single-photon emission computed tomography

Stress single-photon emission computed tomography (SPECT) is a validated imaging tool providing information on the physiological significance of flow-limitation and sarcolemmal membrane integrity. It is also a cost-effective risk assessment tool for major adverse cardiac events in the general and diabetic populations. Moreover, LV function analysis by SPECT enhances its prognostic and diagnostic ability, particularly in the prediction of cardiac death. Reliable automatic algorithms of SPECT provide semiquantitative assessment of myocardial perfusion, LVEF, LV volumes, regional myocardial wall motion and thickening and diastology.

A simultaneous assessment of myocardial perfusion and LV function is important for the diagnosis of cardiomyopathy, particularly dilated cardiomyopathy, and could also be useful in DCM. SPECT can accurately assess both myocardial perfusion and ventricular function in diabetic patients, providing important information for their management. It also has high sensitivity in differentiating ischemic from non-ischemic cardiomyopathy. Nevertheless, factors other than coronary narrowing could play a role in the pathogenesis of myocardial dysfunction in diabetic patients, including endothelial dysfunction, interstitial edema and fibrosis, coronary collateral

circulation, impaired modulation of vascular growth and remodeling. As a result, SPECT could be helpful in these situations.

Positron emission tomography

Among the available imaging modalities, only positron emission tomography (PET) allows quantitative assessment of myocardial blood flow using radiotracer kinetics. However, the combined images by MRI and PET provide a high spatial resolution detection of myocardial metabolic abnormalities and currently represent the most valuable imaging analysis for diagnosis and prognosis in DM. This recent sophisticated imaging modality is also indicated particularly in the case of diabetic patients with or at risk of CAD, since CT is currently considered very reliable in evaluating coronary artery calcium plaque burden and, with the aid of contrast agents, it provides an accurate evaluator of the coronary arterial system.

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EXPERIMENTAL CONTENT

Diffuse myocardial fibrosis in patient with diabetes mellitus type-II (DM-II) assessed by Cardiac Magnetic Resonance T1 mapping technique

ABSTRACT

Purpose: Diabetic cardiomyopathy (DCM) can be cause of a progressive dysfunction of ventricular contractility with the evolution to heart failure, independently of ischaemic heart disease or hypertension. Early stages of DCM are asymptomatic and characterized by various degrees of myocardial fibrosis. Our aim is to non-invasively detect myocardial fibrotic infiltration in DM-II patients, to assess its relationship with ventricular function abnormalities and to compared our results with a group of healthy controls.

Methods and Materials: 100 patients affected by DM-II (57 man, 43 women) with preserved ventricular function and no history of ischaemic disease and 20 matching controls underwent contrast cardiac MR (CMR) between September 2014 and July 2017. Imaging protocol included: modified Look-Locker sequence before and 20 minutes after a double dose of 0.1 mmol/kg gadoterate meglumine injection; T2-mapping; ventricular function module; tagged-cineMR module and late gadolinium enhanced (LGE) imaging. Native myocardial T1 (nT1) and T2 values, extracellular volume fraction (ECV), ventricular torsion angle and myocardial strain values have been calculated and correlated to glycated haemoglobin (HbA1c) and duration of disease. Pearson Correlation, Mann-Whitney test and unpaired T-test were used for statistical analysis.

Results: Patient group had higher nT1 and ECV values compared to controls (1018.29±73.28 ms vs. 975±38 ms, 29.2±0.07% vs. 22.8±4.3% respectively, $p<0.05$ for both), whereas no significant differences occurred in T2 measurements (47.61±2.7ms vs. 47.0±2.8ms respectively, $p=0.23$). nT1 and ECV correlated with HbA1c (nT1: $r^2=0.99$, $p<0.0001$; ECV: $r^2=0,07$; $p<0.005$) and disease duration (nT1: $r^2=0.99$, $p<0.0001$;ECV: $r^2=0,70$ $p<0,001$) in DM-II patients. nT1 and ECV correlate positively torsion (nT1: $r^2=0.31$, $p<0.001$; ECV: $r^2=0.30$;$p<0.001$) and negatively with strain values in tagged-cineMR analysis (nT1 with global longitudinal and circunferential strain: both $r^2=-0.97$, $p<0.0001$; ECV: $r^2=0.63$ and $r^2=0.76$, $p<0.0001$). LGE with ischemic pattern was found in eight patients as marker of silent infarction.

Conclusion: In DM-II patients with preserved ventricular function, HbA1c values and disease duration showed a significant correlation to myocardial nT1 and ECV increase, as reflection of diffuse fibrosis, and geometrical modification.

INTRODUCTION

Diabetic cardiomyopathy (DCM) is defined by the presence of structural and functional abnormalities of the myocardium in diabetic patients without coronary artery disease, hypertension, congenital or valvular heart diseas [1,2].

The development of myocardial dysfunction in diabetes has been attributed to the effects of hyperglicemia: the high levels of advanced glycation end products (AGEs) deposition and oxidation of proteins and lipids are considered as the major pathoges of high glucose-induced cellular injury [3]. These elements in association with microvascular rarefaction and autoimmunity contribute to produce myocardial fibrosis and/or myocardial hypertrophy: chronic myocardial injury results in ventricular remodelling and progressive impairment of myocardial contraction (evolving from diastolic to combined diastolic-systolic dysfunction [4,5].

Early recognition of DCM in pre-clinical stage is currently challenging because patients are usually asymptomatic and ventricular function and morphology remains normal for ages appearing not easily detectable by the conventional cardiovascular imaging exams (echo, CMR and scintigraphy) [6]. In particular subendocarial dysfunction is the first sign of structural changes in DCM and it can be evaluated using conventional Doppler Echocardiography, tissue doppler imaging (TDI) and speckle tracking echocardiography (STE) techniques [7,8]. These methods suffers of some limitations such as high inter and intraobserver variability, angle dependence, noise interference, non discrimination between active and passive motion, irregular ventricular remodelling and wall thinning [8].

Cardiac Magnetic Resonance Imaging (CMR) compare to TEE provides extra-information about myocardial fibrosis and subclinical ischemia, as premature parameters of cardiac dysfunction. CME with the “late gadolinium enhancement” (LGE) technique after injection of contrast medium is considered the reference diagnostic tool for the non-invasively detection “in vivo” of macroscopic myocardial fibrosis in a large spectrum of ischemic and non-ischemic cardiac diseases [9-11]. This technique is very effective in the localization and definition of focal fibrosis but it does not work equally in the detection of diffuse fibrosis and it is burden by the operator dependence [9].

Diffuse myocardial fibrosis can be indirectly assessed through geometrical modifications of myocardial contraction in DCM assessed by the technique of tagging MR [12].

Moreovere the new technique of T1 mapping has been proposed as an objective method to

directly measure the signal intensity of myocardium before the administration of contrast and to measure myocardial extracellular matrix (ECM): this can be quantify in terms of extracellular volume fraction (ECV) after the administration of contrast [13]. It provides histologically-proven evidence of diffuse fibrosis in a broad spectrum of cardiomyopathies, is highly reproducible and sensitive [14-17]. In particular it has been showed a significantly shorter global contrast-enhanced myocardial T1 time in diabetic patients compared with healthy controls and its association with more impaired longitudinal myocardial systolic and diastolic function [18, 19].

In DCM the relationship between T1 mapping parameters, functional and clinical parameters (HbA1c and duration of disease) should be investigate.

The primary aim of our study is to objectively detect and quantify the diffuse fibrotic infiltration of myocardium in a population of patients with diabetes mellitus type II (DM-II) using T1 mapping technique and to compare these results to healthy controls. This study will also examine the correlations between global T1 values (native T1 and ECV) with myocardial function (in term of strain and torsion) and to correlate these results with duration of diabetes and HbA1c levels in order to identify new MR markers of DCM in the asymptomatic phase of the disease and to predict disease progression.

MATERIAL AND METHODS

1.1 Patients enrollment

100 patients affected by DM-II and 20 healthy controls were prospectively enrolled by the Department of Clinical and Molecular Endocrinology between April 2014 and July 2017 and classified in gender-based age-matched groups.

Inclusion criteria were: age 35-75 yrs; HbA1c < 10%; normal blood pressure (BP) or hypertension under pharmacological control by at least 5 years; BMI < 40; diagnosis of diabetes mellitus > 3 years.

MR Exclusion criteria: standard contraindication to Magnetic Resonance; age < 18 years; severe arrhythmia or tachycardia; history of significant coronary artery disease, previous myocardial infarction or cardiac inflammatory disease; history or evidence systemic autoimmune disorders, sarcoidosis, amyloidosis or congenital heart disease; history or evidence of uncontrolled

hypertension; chronic Kidney disease Stage 4 and 5 (GFR < 30 mL/min/1.73m^2)

All patients underwent blood test, physical examination and measure of anthopometric parameters prior the MR examination. Moreover all patients underwent ad ECG and Transthoracic Echocardiography (TTE) in order to satisfy inclusion criteria. TTE inclusion criteria are summarized in Table 1.

Table 1. TTE inclusion criteria

Diastolic function	**I grade**
Systolic function	FE >45<55%
Regional contraction	Absence of akinesia or dyskinesia
Thickness of SIV	>11 mm in man and >10 mm in women
Valvular stenosis/insufficiency	mild
Aneurism	no

Non-diabetic subjects with normal LV function and normal value of glycosylated haemoglobin (< 3.5 %) were enrolled as a control group; there were included patients previously scheduled for CMR with other indications, such as arrhythmogenic right ventricular dysplasia, non-compaction cardiomyopathy or atrial fibrillation and with CMR negative results.

All subjects that during the CMR exam showed evidence of macroscopic late enhancement myocardial areas indicative for fibrosis/scar from previous myocardial infarction were excluded.

Consent of the local ethical comity was obtained and all informed consents of patients on the study were collected.

1.2 Cardiovascular Magnetic Resonance

All patients underwent a contrast cardiac MR study (CMR) in our Department using a 1.5 T scanner (Siemens Avanto, Erlangen, Germany).

All patients and healthy controls underwent a CMR exam using the following protocol:

- Breath-hold ECG-gated balanced-steady state free precession (bSSFP) cine-MR sequences in standard fashion, according to the true anatomic axes of the heart, to assess bi-ventricular morphology and function;
- Tagging cine-MR sequences, acquired in short axis, to assess strain and torsion;
- T2 STIR sequences were acquired on a basal, mid and apical plane in order to rule out the presence of myocardial edema;
- T2 mapping sequences were acquired on the same basal, mid and apical plane to validate the absence of myocardial edema;
- First pass imaging were acquired during the injection of 0.1 mmol/kg of Gadoterate meglumine.
- Early gadolinium enhanced images were acquired by performing T1-weighted turbo spin echo sequence in four identical axial slices both before and three minutes after intravenous administration of the first bolus of contrast medium in order to evaluate early myocardial enhancement.
- Novel Modified Look-Locker Inversion recovery sequences (MOLLI) were acquired on a mid-ventricular short axis view before contrast administration and after a double injection of 0.1 mmol/Kg of gadolinium (the second injection was done 3 minutes after the first one) at 3, 5, 10, 15 and 20 minutes in order to estimate the Extracellular volume fraction (ECV).
- Traditional contrast-enhanced T1-weighted inversion recovery images were acquired between 15 and 20 minutes after CM injection on short-axis view using the same image geometry as for the MOLLI sequences for late gadolinium enhancement imaging (LGE).

Parameters of all sequences are summarized in Table 2.

Table 2. MR sequences parameters

	T2 STIR	T2 mapping	T1 mapping pre	CINE	CinelPAT	Cine-Tagging	T1 morph	FIRST PASS	T1 mapping post	TI scout	T1
TA	12 s	12s	12s	65/12	13s	1.31'	1.27'	1:12	11s	28s	12s
Thickness	10mm	8mm	8mm	8 mm	6 mm	8mm	6mm	8mm	8mm	8 mm	8mm
Gap	50%	20%	20%	25%	20%	25%	25%	150%	20%	20%	20%
Matrix	256x143	192x75	256x66	256x146	320x260	256x70	256x80	128x78	256x66	192x78	256x160
TE	75ms	1.1ms	1.09ms	1.21ms	1.26ms	3.2ms	23ms	0.96ms	1.09ms	1.12	4.33
TR	900ms	235.4ms	331.94ms	51.3ms	44.7ms	46.83ms	700ms	174ms	331.94ms	23ms	700
Flip angle	180°	12°	35°	70°	80°	15°	16°	15°	35°	50°	30°

1.3 Imaging evaluation

All images were evaluated by two double-blinded observers using a cardiac dedicated software (CMR 42, Circle Cardiovascular Imaging, Canada).

1.3.1 Ventricular function analysis

For the ventricular volumes analysis, the epi- and endocardial contours of the left ventricle were drawn on b-SSFP cineMR images at end-diastole and end-systole in order to measure end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and myocardial mass (MASS); all values were indexed for antropometric data (body mass index).

1.3.2 Tagging analysis

HARP software tool was used on these images for evaluating myocardial strain and torsion. The epi- and endocardial contours of the left ventricle were drawn on tagging-cineMR images in a single phase for each sequences. The software automatically generated 24 points for each contour drawn and it is extended for each place on short axis view.

Torsion angle between basal and apical planes was calculated as an average of rotation of each points. Global torsion of left ventricle (θ°) has been calculated as the difference between positive rotation of the apex and negative rotation of the basis: θ= θ apice – θ base. The greater systolic torsion was measured as the greated value of θ during all cardiac cycle.

1.3.3. T2 STIR analysis

The epi- and endocardial contours of the basal, middle and apical planes acquired on left ventricle were drawn on T2-STIR images and a reference ROI was put on skeletal muscle (i.e. perctoralis muscle) and T2 ratio was calculated as previously published [20].

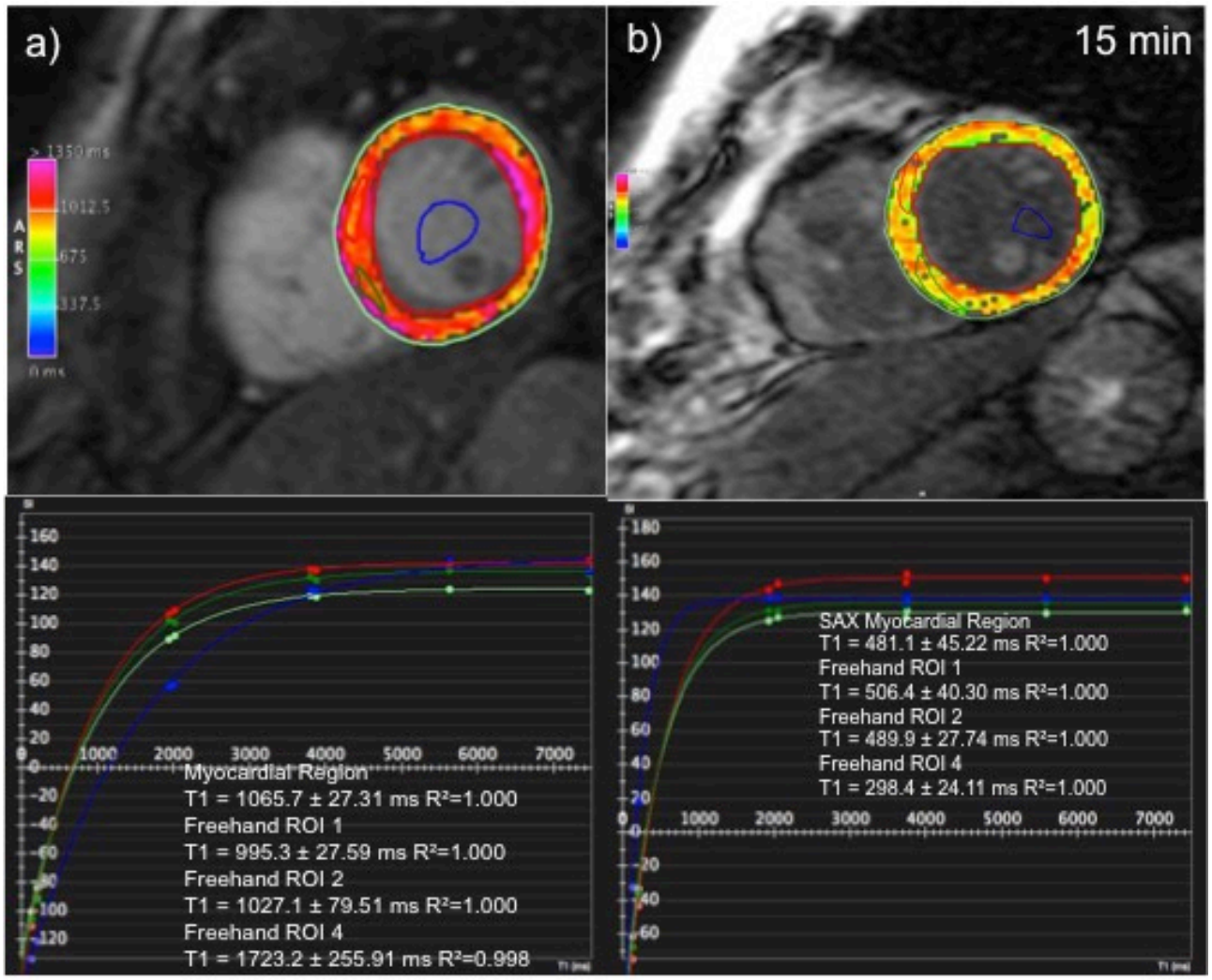
1.3.4. *T2 mapping analysis*

On T2 map a ROI was drawn on interventricular septum on the basal, middle and apical planes acquired on left ventricle.

1.3.5. *T1 mapping analysis*

For the T1 mapping analisis the epi- and endocardial contours of the left ventricle were drawn on basal, middle and apical planes using as a reference the blood into left ventricle on both pre-contrast (native T1 of myocardium, nT1) and post-contrast images (Extracellular Volume Fraction, ECV) according to the note formule [21] (Figure 1).

Figure 1: T1 mapping: a) Pre-contrast measurement; b) post-contrast



1.3.6. LGE analysis

LGE images were qualitatively assessed in order to detect the presence of macroscopic myocardial areas of enhancement with coronary distribution and subendocardial involvement suggesting a previous myocardial infarction, as this is an esclusion criteria. However, patients with little focal areas of enhancement in other locations were included as these abnormalities may represent small fibrotic areas as result from hyperglycemia or due to small ischemic injury.

1.4 Correlation between cardiac function, T1 mapping and ECV with clinical data.

All data collected on cardiac function (strain, torsion), T1 mapping and ECV values were compared to HbA1c levels and duration of disease. In order to assess if there are any difference between DM patients without hypertension and DM patients with hypertension all study population was divided in two subgroups and T1 mapping values were separately compared to HbA1c levels and duration of disease. Moreover all data collected were compared between DM II patients and controls.

1.5 Statistical analysis

Statistical analysis was done using SPSS Software for Windows,version 20.0 (SPSS,Inc,Cary,NC package). All continuous variable were expressed as average±SD. All correlations were done by calculating the Pearson's correlation coefficients and differences between DM II patients and controls were done using the unpaired t test for normal distribution of data or the Mann-Whitney test for non-normal distribution. There were considered statistical significant only P value<0,005.

RESULTS

1.1 *Study population*

100 patients affected by DM-II (57 man, 43 women; mean age 64,7+7,3 yo) and 20 healthy controls underwent contrast cardiac MR between September 2014 and July 2017. All features of DM-II patients were summarized in Table 3 and 4.

Table 3. Features of study population

Features	**Women** **N =43**	**Man** **N = 57**	**P**
Age	66.8 ± 5.1	64.2 ± 8.3	0.60
BMI	28.9 ± 4.1	28.4 ± 3.7	0.63
Waist Circumference cm	99.8 ± 8.5	103.1 ± 9.7	0.29
Glycemia mg/dL	133.7 ± 43.1	145.6 ± 45.2	0.21
HbA1c %	6.7 ± 1.0	6.9 ± 0.9	0.32
Trunk fat * %	34.5 ± 3.6	24.1 ± 4.5	0.00
CrCl mL/min	94.5 ± 26.6	114.6 ± 36.5	0.19
ASP mmHg	129.4 ± 16.3	124.7 ± 13.1	0.48
ADP mmHg	71.6 ± 9.1	73.8 ± 8.9	0.32
HR batt/min	74.5 ± 12.6	67.9 ± 7.6	0.08
Age of disease DM2	11.9± 8	13.2 ± 8.1	0.90

BMI, Body Mass Index; CrCL, Creatinine Clearance; ASP, arterial systolic pressure; ADP, artedial dyastolic pressure; HR, Heart rate

Table 4. Comorbidities of study population

Comorbidy	**Women (43)**	**Man (57)**	**p**
Hypertension	26 (61.9)	32 (61.5)	0.97
Carotid atherosclerosis	5 (11.9)	16 (30.8)	0.45
Dislipidemia	30 (71.4)	34 (61.5)	0.66
Hypogonadis age-related	42 (100)	8 (15.4)	0.00
Complications	**Women %**	**Man %**	**p**
Diabetic Nephropathy	5 (11.9)	12 (23.1)	0.49
Diabetic Neuropathy	5 (11.9)	10 (19.2)	0.3
Diabetic Retinopathy	4 (9.5)	2 (3.8)	0.4

11 (11%) patients were excluded from the analysis: 8 (8%) because of the evidence of macroscopic late enhancement myocardial areas indicative previous myocardial infarction; 1 (1%)because of the evidence of lung mass (resulted at biopsy as a lung cancer) and 2 (2%) patients decided to stop the MR examination because of fatigue.

1.2 Imaging evaluation

Functional results, including tagging-MR results, were showed in Table 5.

Table 5. Functional results of left ventricle

Left ventricle Function			
	DM II (n=57)	Controls (n=43)	p
LV-EDVi (mL/m^2)	55.02±13.8	55±9.2	n.s.
LV-ESVi (mL/m^2)	21.6±8.3	18±8.3	n.s.
LV-SVi (mL/m^2)	69.2±8.3	51±10.8	n.s.
LV-EF (%)	62.6±7.5	68±6.9	n.s.
LV-Mass(g/m^2)	**80.7±10.7**	**66±10.9**	**< 0.05**
Global Radial Strain (%)	51.5±11.5	43.2±9.3	< 0.01
TD (mm)	**46.6±5**	**43.2±25**	**0.003**
IVS (mm)	**11.2±2.2**	**10.2±2**	**0.001**
Time-to-peak Radial Strain (ms)	299.2±38.2	322.5±48.7	< 0.05
Global Circumferential Strain(%)	**-22.5±5.3**	**-20.5±3.6**	**< 0.01**
Time-to-peak Circum Strain (ms)	3013±41.8	322.6±48.7	< 0.05
Global Longitudinal Strain (%)	**-18.4±4.4**	**- 24.4±4.3**	**< 0.01**
Time-to-peak Long Strain (ms)	321.6±50.6	310.8±49.8	< 0.05
Torsion (°)	**13.7±3.4**	**14.4 ± 1.1**	**< 0.05**

T2 ratio and T2 mapping

Nobody of DM II patients showed myocardial edema on T2 images or early Gd enhancement after intravenous administration of the first bolus of contrast agent.

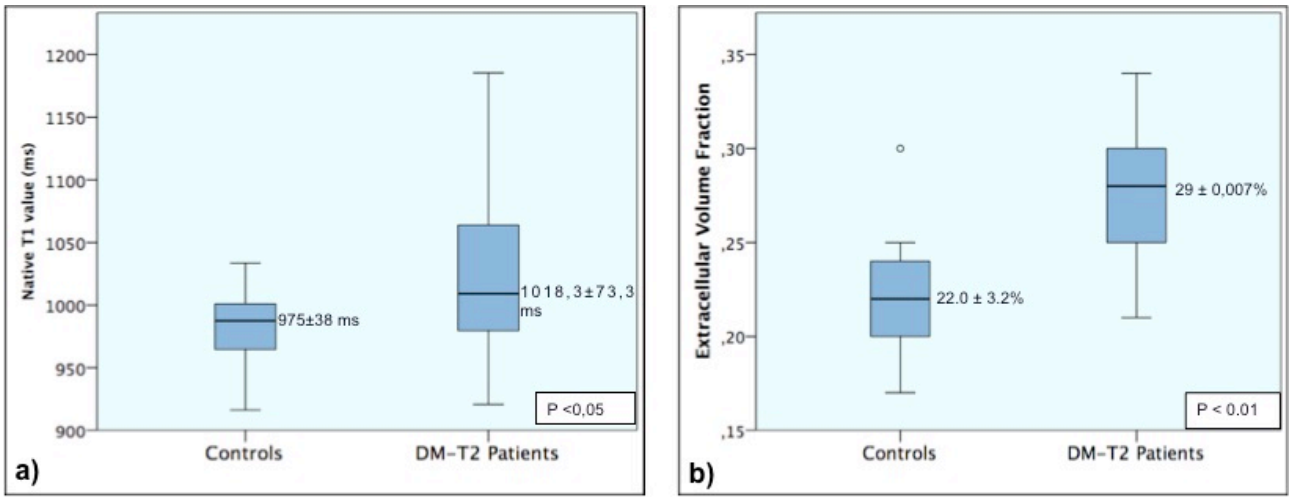
T2 mapping images showed no significant difference between DMII patients and controls (average of 47.6±2.7 ms in DM II vs 47±2.8 in control group.

T1 mapping

nT1 mapping images showed values of 1018,29±73,28 ms in DM-II vs 975±38 ms controls (p<0.005) (Graph 1). Post-contrast T1 values at 15' were of 408,94±51,89 ms.

ECV values in DM-II patients were of 0,29±0,007 compare to controls in which were of 0,22±3,2 (Graph 1).

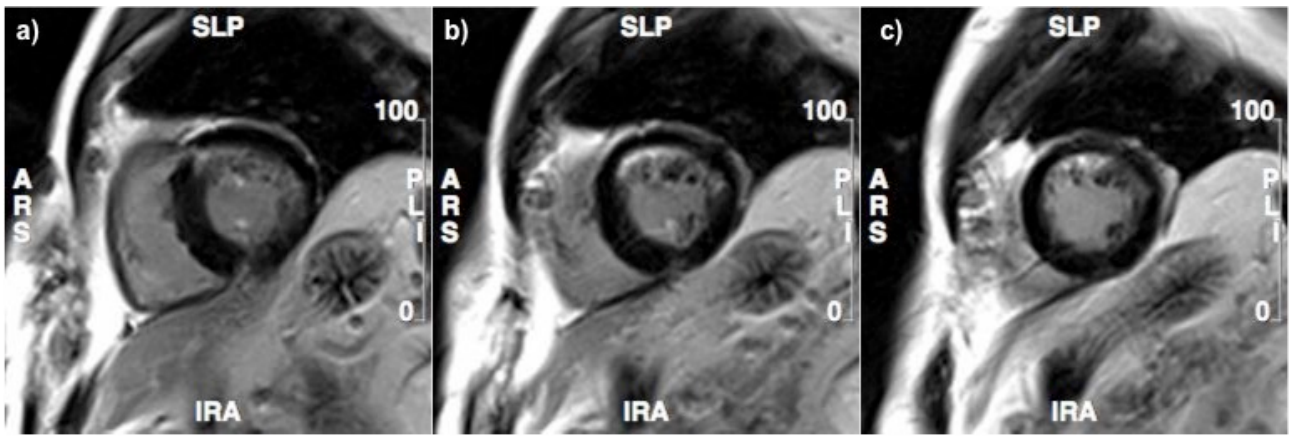
Graph 1. (a) Correlation of nT1 values between DM-II patients and Controls and (b) Correlation of ECV values between DM-II patients and Controls



Late Gadolinium Enhancement

LGE images showed macroscopic area of fibrosis due to myocardial infarction in 8 patients while in 7 there were shaded area of aspecific fibrosis (Figure 2).

Figure 2. Silent myocardial infarction discovered during MR examination in 67 yo man affected by DM-II. Late Gadolinium Enhancement images showed un anterior myocardial infarction extended on a) basal, b) middle and c) apical planes.



1.3 Correlation between cardiac function, T1 mapping and ECV with clinical data.

There was an inverse correlation between T2 map values in DM II patiens and HbA1c values (7.5±0.9; r=-0.46; p<0.0001), while no correlation was observed with duration of disease.

nT1 values showed a significant correlation with HbA1c levels (r^2=0,99 p<0,0001) and with duration of disease (r^2=0,99 p<0,0001).

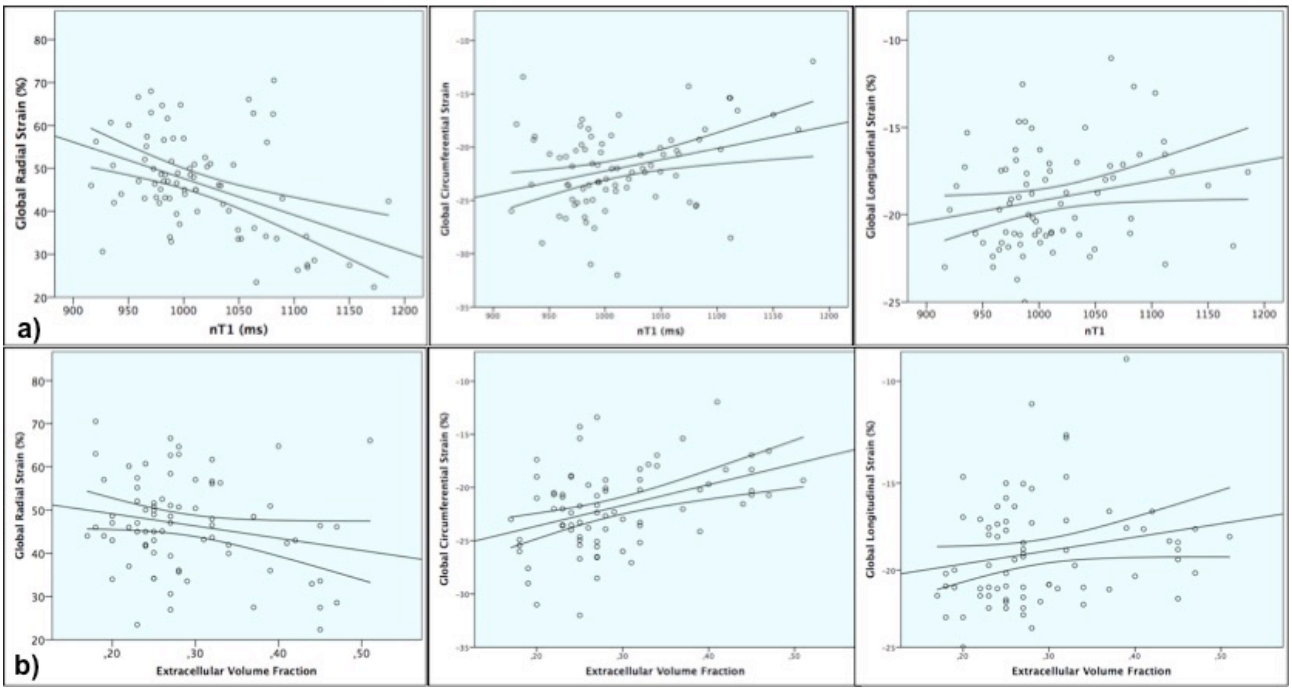
ECV at 15' showed a significant correlation with HbA1c levels (r^2=0,07 p<0,005) and with duration of disease (r^2=0,70 p<0,001).

Correlations between left ventricle function and nT1 and ECV were displayed in Table 6 and Graph 2.

Table 6. Correlation between left ventricle function and nT1 and ECV

	nT1		ECV	
	R	p value	R	p value
GRS	-0.77	<0.0001	0.67	<0.0001
GCS	-0.97	<0.0001	0.63	<0.0001
GLS	-0.97	<0.0001	0.76	<0.0001
Torsion	0.31	<0.001	0.30	<0.001
TTP Torsion	-0.18	0.33	0.18	0.04

Graph 2. Correlation between nT1 (a) and ECV (b) vs Radial, Circumferential and Longitudinal Strain



No significant differences were found between nT1 and ECV in DM-II patients without hypertension and DM-II patients with hypertension (p=0.70; p=0,67).

DISCUSSION

DCM as a clinical entity remains unclear despinte many investigations have been done. It is defined as myocardial dysfunction that occurs independently of coronary artery disease, valvular pathology or hypertension. It has been associated with modifications of left ventricle geometry, altered function and tissue abnormalities [1, 4].

In our study we found significant differences between nT1 and ECV in DM-II patients versus controls. In particular the difference in ECV between DM-II patients and controls confirmes previous studies [22] suggesting that extracellular matrix expansion could be considered an important intermediate phenotype in diabetic patients detectable by ECV and treatable. The increase of ECV in DM-II is due to proliferation of myofibroblast activated by glucose and myocardial fibrosis [6]. Moreover ECV in diabetic people is associated with subclinical cardiac dysfunction [23], it is associated with higher rate of adverse outcomes in the setting of diabetes. In literature results on ECV and DCM are controversial [24]: DM-II is expected to be associated with

high value of ECV, but some studies showed similar results between DM-II patients and control [25, 26]. In these studies patient population consisted of young adults or selection criteria were too much limited.

nT1 and ECV showed a significant correlation with HbA1c and in particular with duration of disease. Fibrotic changes in myocardium are associated with duration of disease in animal and human studies and ECV may be more sensitive than native and postcontrast T1 in the confirmation of these structural changes [27, 28]. The relationship between diabetic history and ECV indicates that ECV may represent the long-term effects of DCM on the myocardium.

In our study the correlation with HbA1c suggested a possible role of HbA1c as a marker of time-averaged glucose level. Hyperglycemia can cause persistent (a few days) damage to cells by disrupting the signal feedback loop [xx] and hyperglycemia can promote the proliferation of cardiac fibroblast [29, 30]. This result is in conflict with previous studies in which no correlation was found between fibrosis and HbA1c and for this reason we think that it should be investigate in future studies on bigger population of diabetic patients [31].

No significant differences were found between nT1 and ECV in DM-II patients without hypertension and DM-II patients with hypertension (p=0.70; p=0,67) and this result support the idea that farmacological control of hypertension enables to stop or slow down the progression of DCM. On the other hand uncontrolled hypertension is associated with progression of DCM as it has been investigated in previous studies [32].

Our results showed a significant relationship between impaired left ventricle contractility measured by tagging and the increased ECV despite the EF conserved in DM-II patients. These data confirmed a previous study done by our group on DM-II patients [12] in which we found an uncoupling between longitudinal and circunferential strain and a resultant modification of torsion angle of left ventricle as indirect signs of elevated myocardial collagen content. This this correlation adds value to T1 mapping technique. In future it should be considered the new feature tracking technique for strain and torsion measurements: by this technique is it possible to obtain measurement of myocardial contractility directly on cine sequences (bSSFP) adquired in short axis, 4-chamber and long axis view and in this way it will be possible reduce MR scan time.

LGE observed in 8 DM-II patients confirmed the capability of CMR to see macroscopic area of fibrosis due to silent myocardial ischemia (SMI) or myocardial infarction (MI). This entity is an

important clinical entity, it is common in patients with diabetes and it is an independent predictor of mortality [33]. Its recognition may lead to early intervention and changes prognosis of these patients. In a substudy of the Diabetes Control and Complications Trial it has been demonstrated a 4.3% prevalence of LGE consistent with unrecognized MI in patients with type 1 diabetes without clinical evidence of cardiovascular disease [34]. Moreover recognition of MI is associated with poor glycemic control, diabetic nephropathy, elevated circulating levels of HbA1c and albuminuria both in DM-II and DM-I [35]. In our study all patient with MR signs of MI had glycemic control but they showed a trend of higher levels of HbA1c.

Nobody of DM II patients showed myocardial edema on T2 images and T2 mapping values confirmed the absence of edematous changes in myocardium. We used T2 mapping to verify results of the standard measurements done with T2-STIR images [36]. Moreover there were no significant difference between DM II patients and controls.

Our study has some limitations: first of all we need to collect data on a bigger population of diabetic patients; second we did not recruit patients with a GFR ≤ 30 mL/min/1.7m2 , and it should be interesting to assess nT1 values also in DM-II patients with impaired renal function and who cannot undergo CMR with contrast: the measurement of nT1 could be proposed as an important marker of DCM in these patients. Third we did not exclude coronary artery disease by coronary angiography in all DM-II patients and this elements may have introduced a bias. Fourth we did not correlate our results with circulating biomarkers. Moreover further research should be done on gender differences in DM-II patients in functional parameters, nT1 and ECV and to correlate these with clinical and laboratory markers.

CONCLUSION

DM-II patients showed higher nT1 and ECV values compared to controls using the technique of T1 mapping. This method could be useful in the detection of interstitial fibrosis and in the early diagnosis of DCM. In particular it could add value to the technique of MR-tagging because of its correlation with contractile function. Moreover T1 mapping values correlated with duration of disease and HbA1c.

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